REMARKS

This is in response to the Office Action that was mailed on January 28, 2005.

Claims 1, 6, 12, and 13 are amended to delete a clause which the Examiner has characterized as new matter. The claims are also amended slightly to improve their clarity. Claims 1 and 13 are amended to recite that no protease inhibitor to inhibit degradation of natriuretic peptides is added to the specimen. This language is amply supported by the disclosure. For instance at page 2, lines 11-13:

> To date, some protease inhibitors ***were*** added into the samples ***for the inhibition of the degradation of natriuretic peptides***. (emphasis supplied).

Page 4, lines 2-4:

> Materials inhibiting the activation of a substances degrading peptides' mean[s] materials, which can inhibit the activation of substances degrading the peptides, such as proteases etc. … .

Page 4, lines 20-23:

> Although aprotinin has been added into specimens to inhibit the degradation of natriuretic peptides by proteases which are already active in blood or are activated after blood collection, it can not inactivate them contained in biological samples completely.

That the present inventors conceived of the present invention as ***avoiding*** the addition of such protease inhibitors is shown by the following textual quotations from the specification:

At page 3, lines 2-9:

> These results suggest that the degradation of natriuretic peptides in specimens can be suppressed by using a container wherein the face coming into contact with specimens is made of a material inhibiting the activation of a substance degrading the peptides upon handling specimens containing mammalian natriuretic peptides. Therefore, it is expected that the former complicated handling of specimens can be eliminated by using a container wherein the face coming into contact with specimens is made of materials other than glass upon the measurement of natriuretic peptides.

At page 3, lines 18-22:

> This invention relates to a method for inhibiting the degradation of mammalian natriuretic peptides by using a container wherein the face coming into contact with specimens made of a materials, preferably, silicone or plastic, which inhibits the activation of the substances degrading the peptides.

Page 4, lines 18-19:

> This invention relates to a measurement of natriuretic peptide in specimens which do not contain aprotinin.

Thus it is plain that the inventors conceived of and describe as their invention a method for inhibiting proteases in a sample by use of a silicone or plastic tube, thereby eliminating the need for adding any protease inhibitor that inhibits degradation of

natriuretic peptides, such as aprotinin (a species of such a protease inhibitor), to the sample.

No new matter is introduced by this Amendment. Entry of this Amendment - in order to place the application into condition for allowance or into better condition for appeal - is respectfully solicited. Claims 1, 3, 6, 12 and 13 are pending in the application.

In a telephonic discussion between Examiner Gitomer and Applicants' representative Mark Nuell on April 4, 2005, Examiner Gitomer indicated that he would consider arguments that the absence of protease inhibitors is adequately described in the specification and arguments that the presently claimed invention involves unexpected results with respect to the prior art of record.

THE INVENTION. The present invention involves the discovery that degradation of brain natriuretic peptide (BNP) in a specimen can be inhibited by a process that comprises collecting the specimen containing BNP into a container, wherein a face of the container coming into contact with the specimen is made of or coated with a material selected from the group consisting of silicone and plastics. In accordance with the present invention,

no protease inhibitor for inhibition of the degradation of natriuretic peptides is added to the specimen. EDTA may be used in connection with the present invention in order to inhibit blood clotting. While it is known that due to its chelating effect, EDTA may function as a metalloprotease inhibitor, EDTA is not a "protease inhibitor for inhibition of the degradation of natriuretic peptides". In accordance with the present invention also, the proportion of residual brain natriuretic peptide immunoreactivity is 50% or more after 24 hours standing at 25°C.

THE PRIOR ART. The International Search Report, filed herein on April 24, 2000, cited three references: *Clinical Chemistry* 42:1627-1633 (Clerico); *Biochemical and Biophysical Research Communications* 161:1177-1183; and *Pharmacology & Toxicology* 68:276-281 (Lindberg). In the International Preliminary Examination Report which was filed herein on July 11, 2000, the International Preliminary Examination Authority refers to the disclosure of the Clerico et al. article. However, the IPER concludes that "a technique using a container made of or covered with a material containing a substance capable of inhibiting ***the activation of*** a peptide-decomposing substance is ***neither described nor suggested*** in any of the documents cited in the ISR". (Emphasis supplied.)

Neither Clerico nor Lindberg teach that the degradation of BNP

in a specimen is inhibited by placing the specimen into a container made of or coated with a material selected from the group consisting of silicone and plastics. The present claims expressly require, among other things, that *the ratio of* ***BNP immunoreactivity is 50% or more after 24 hours standing at 25°C.*** Lindberg relates to purified ANP. Also, the specimens studied by Lindberg et al. were not bodily samples. The Clerico et al. article indicates that after incubation at 37°C for 30 minutes the specimen without protease inhibitors showed 70.2% degradation. Clerico et al. concluded that aprotinin is necessary for inhibiting the degradation of ANP. The Clerico et al. reference fails to disclose or suggest the ***unexpected result*** that residual BNP immunoreactivity can be 50% or more even when a protease inhibitor such as aprotinin is not added to the specimen if the BNP is present in a sample held in a plastic or silicone tube.

THE REJECTION. Claims 1, 3, 6, 12, and 13 were rejected under the first paragraph of 35 U.S.C. §112 as failing to comply with the written description requirement. Specifically, the Examiner asserts that the clause "excluding the addition of any inhibiting agents which inhibit the degradation of brain natriuretic peptide" is new matter and is not supported by the specification as originally

filed. While Applicants do not agree with the Examiner in this regard - for reasons of record in previous submissions herein - the clause in question is now deleted from the claims. Accordingly, this ground of rejection is obviated by the present Amendment.

Conclusion

Applicants respectfully submit that the above remarks and/or amendments fully address and overcome the outstanding rejections. For the foregoing reasons, Applicants respectfully request the Examiner to withdraw all of the outstanding rejections, and to issue a Notice of Allowance indicating the patentability of the present claims. Early and favorable action of the merits of the present application is thereby respectfully requested.

If there are any minor matters precluding allowance of the present application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Richard Gallagher (Reg. No. 28,781) at (703) 205-8008.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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